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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,826	10/17/2006	Catherine M. Verfaillie	89003-2006.1	2871

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EXAMINER	
WANG, CHANG YU	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,826	VERFAILLIE ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/22/05* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *notice to comply*.

DETAILED ACTION

Sequence Rules

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825. Specifically, no sequence identification has been provided for the amino acid sequences and nucleic acid sequences presented in Figure 4 and Table 1 of the instant specification. In case these sequences are new, Applicant needs to provide a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, a substitute paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). The instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. See M.P.E.P. 2422.04.

The text of the instant specification (pages 5 and 20) is not in compliance with the requirements for Sequence Identifiers (see MPEP 2422.03). The appropriate format

for sequence identifiers is SEQ ID NO: X, wherein "X" is the sequence number.

Appropriate correction is required.

Status of Application/Election/Restrictions

2. Applicant's election with traverse of Group I, bone marrow and dopaminergic neurons in the reply filed on November 19, 2007 is acknowledged. The traversal is on the ground(s) that Groups I and II are linked and the claimed species are related. In addition, Applicant argues that a search for Groups I and II is not a burden because a search for Group I would include that for Group II and a search for all of the claimed species is also not a search burden. This is not found persuasive because the instant application is a 371 national stage application and Applicant's inventions do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features.

MPEP 201 "NATIONAL APPLICATIONS (35 U.S.C. 111) VS. NATIONAL STAGE APPLICATIONS (35 U.S.C. 371)" states that "Treatment of a national application under 35 U.S.C. 111 and a national stage application (a national application which entered the national stage from an international application after compliance with 35 U.S.C. 371) are similar but not identical. Note the following examples: (A) Restriction practice under MPEP § 806 + is applied to national applications under 35 U.S.C. 111(a) while unity of invention practice under MPEP Chapter 1800 is applied to national stage applications".

As previously made of record, Group I was found to have no special technical feature that defined the contribution over the prior art of WO02086073 (published Oct 31, 2002.) and US6284539 (issued on Sept 4, 2001). Thus, Group I cannot share a special technical feature with the other claimed inventions. Accordingly, Applicant's inventions do not contribute a special technical feature when viewed over the prior art, they do not have a single inventive concept and thus lack unity of invention. In addition,

although related inventions may be searched together, it is under a condition that these inventions satisfy the requirement of unity of invention. However, this is not the case for the instant application. In summary, although Groups I and II are related to product and process, Applicant's inventions have no unity of invention. The subject matter of Groups I-II requires different searches and analyses, which would be a burden to the examiner.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-13 are pending. Claim 12 is withdrawn with traverse (11/19/07) from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-11 and 13 are under examination with respect to bone marrow and dopaminergic neurons in this office action.

Information Disclosure Statement

4. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

5. The use of the trademarks (see p.7, 11 and 12) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is indefinite because the claim contains the trademark/trade name N2 supplement®. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the

trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a N2 supplement for a culture medium and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7, 9, 11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO02/086073 (Studer et al., published Oct 31, 2002, cited in office action mailed 10/18/07) in view of US2003/0211605 (Lee et al., published Nov 13, 2003, priority May 1, 2000).

Independent claims 1 and 13 are directed to a method for inducing stem cells to differentiate into neuronal cells comprising culturing stem cells with bFGF, FGF8, Sonic Hedgehog (Shh), BDNF and co-culturing the stem cells with astrocytes. Claims 2 and 3

depend from claim 1, which are limited to addition of a supplement comprising insulin, transferring, selenite, putrescine and progesterone (claim 2) and N2 supplement (claim 3) in the method of the claim 1. Dependent claim 4 recites "at least 7 days for each step" in the method of the claim 1. Dependent claims 5-10 recite stem cells from different sources including bone marrow. Dependent claim 11 recites specific neurons.

WO02086073 teaches a method of inducing stem cells to differentiate into neuronal cells comprising culturing embryonic stem cells in the presence of bFGF, FGF8, Shh, BDNF and co-culturing the cells with astrocytes as recited in instant claims 1 and 13. (see p. 4, paragraph 12-p. 6 paragraph 20; p. 24, example 2-p. 30, in particular). WO02086073 teaches a method of expanding embryonic stem cells isolated from embryonic or adult tissues in a DMEM+F12 medium comprising bFGF, FGF8, Shh, BDNF, N2 supplement (claim 2), insulin, transferrin, selenite (part of claim 3) and fibronectin as recited in instant claims 2-3 (part of the claim 3) (see p. 25-26, paragraphs 75-78, in particular). WO02086073 teaches differentiation of cultured embryonic stem cells into neurons and astrocytes, which meets the limitation of "comprising co-culture astrocytes" as recited in instant claims 1 and 13 (see p. 25-26, paragraphs 75-78, in particular). WO02086073 also teaches that the cultured stem cells are mammalian stem cells, human stem cells, neural stem cells, embryonic stem cells, embryonic germ cells and brain as recited in instant claims 5-7 and 9 (see p. 12, paragraph 49; p. 19 paragraphs 63-p.20). WO02086073 also teaches differentiation of stem cells into dopaminergic, serotonergic, GABAergic neurons and combinations thereof as recited in instant claim 11 (see p.12, paragraph 48; p17, paragraph 59, in

particular). In addition, although WO02086073 does not explicitly teach at least 7 days for each step as recited in instant claim 4, each step and each stage of the culture conditions of WO02086073 require 6-9 days and the whole culture procedures take more than one month (see p.27-29, in particular), which is within the limitation of the instant claim 4. But WO02/086073 does not teach a supplement comprising insulin, transferrin, selenite, putrescine and progesterone as recited in instant claim 2.

US2003/0211605 teaches a method of inducing stem cells to differentiate into neuronal cells comprising culturing embryonic stem cells in the presence of bFGF, FGF8, Shh, and co-culturing the cells with astrocytes as recited in instant claims 1 and 13 (see abstract; p. 9, [0116]-p. 10, [0129]; p. 2, [0016]-[0021]; p.3, [0040]-[0043]; p.4, [0045]-[0048], [0058]; p. 5, [0071]-p.7,[0093];p.11 [0147]-[0148]; p. 13, example 1-p. 16, example 7, in particular). US2003/0211605 teaches a method of expanding embryonic stem cells and the CNS precursor cells in a DMEM plus F12 medium comprising bFGF, FGF8, Shh, N2 supplement, insulin, transferrin, selenite, putrescine, and progesterone as recited in instant claims 2-3 (see p.9, [0123]-[0126], in particular). US2003/0211605 teaches differentiation of cultured embryonic stem cells into neurons using the same medium in presence of ascorbic acid and the differentiation of stem cells encompasses 3% astrocytes, which meets the limitation of "comprising co-culture astrocytes" as recited in instant claims 1 and 13. Although US2003/0211605 does not explicitly teach at least 7 days for each step as recited in instant claim 4, the complete culture procedures of US2003/0211605 take more than one month (see p.8, [0111], in particular), which meets the limitation of the instant claim 4. US2003/0211605 also

teaches that the cultured stem cells are mammalian stem cells, human stem cells, neural stem cells, embryonic stem cells, embryonic germ cells and brain as recited in instant claims 5-7 and 9 (see p. 4, [0051]). US2003/0211605 also teaches differentiation of stem cells into dopaminergic, serotonergic, GABAergic neurons and combinations thereof as recited in instant claim 11 (see p.9, [0125]-p.10,[0127], in particular). US2003/0211605 also teaches BDNF to promote survival and function of neurons and glial cells (0070]-[0071] or cells transfected with BDNF gene to promote survival and function of neurons ([0177]).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to incorporate the teachings of US2003/0211605 to add a supplement as recited in instant claim 2. The person of ordinary skill in the art would have been motivated to do so because US2003/0211605 has taught a method of inducing differentiation of stem cells into neurons in a culture medium comprising bFGF, FGF8, Shh, N2 supplement, insulin, transferring, selenite, putrescine, and progesterone. Thus, one of ordinary skill in the art would have an expectation of success in differentiation of stem cells into neurons by adding the supplement of the instant claim 2 in the method of WO02/086073.

Note that

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980); see also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992). See MPEP § 2144.06.

8. Claims 1-11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO02/086073 (Studer et al., published Oct 31, 2002, cited in office action mailed 10/18/07) in view of US2003/0211605 (Lee et al., published Nov 13, 2003, priority May 1, 2000) as applied to claims 1-7, 9, 11 and 13 above, and further in view of Song et al. (Methods in Mol. Biol. 2002. 198: 79-88).

WO02/086073 and US2003/0211605 are as set forth above at paragraph 7 but do not teach multipotent adult progenitor cells and bone marrow as recited in instant claims 7-10.

Song et al. teach a method of culturing and differentiating bone marrow and umbilical cord blood cells into neural progenitor cells and neurons in a DMEM/F12 medium comprising FGF-2/bFGF, EGF, transferrin, insulin, putrescine, progesterone, selenium, trans-retinoic acid, BDNF and NGF (see p. 80). Song et al. also teach culturing human and mouse bone marrow and human umbilical cord cultures (p. 82-83). The bone marrow and umbilical cord blood cells encompass stem cells and nonhematopoietic progenitor cells from bone marrow are mesenchymal stem cells or bone marrow stromal cells as taught by Song et al. (p.79), which meet the limitations of multipotent adult progenitor cells (MAPCs) and bone marrow as recited in instant claims 7-10.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to differentiate stem cells that are derived from multipotent adult progenitor cells (MAPCs) and bone marrow into neurons by using the culture conditions of WO02/086073 and US2003/0211605. The person of ordinary skill in the art would

have been motivated to do so because multipotent adult progenitor cells (MAPCs) and bone marrow have been shown to encompass stem cells that are able to be induced to differentiate into neurons as taught by Song et al., and WO02/086073 and US2003/0211605 have taught that stem cells can be induced to differentiate into neurons in the claimed culture conditions. Thus, the person of ordinary skill in the art would have an expectation of success in culturing and differentiating stem cells derived from bone marrow and MAPCs into neurons in the culture conditions of WO02/086073 and US2003/0211605.

Conclusion

9. NO CLAIM IS ALLOWED.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

US 6284539 (cited in the previous office action) teaches a method of differentiating neural stem cells into dopaminergic neurons under a culture condition containing FGF8, sonic hedgehog, BDNF and astrocytes.

US Patent No. 7129034 (Yu et al., issued Oct 31, 2006, priority Oct 25, 2001) teaches a method of culturing and differentiating bone marrow cells into neural progenitor cells and neurons in a culture medium comprising FGF-2 and EGF.

11. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
January 24, 2008

JEFFREY STUCKER
SUPERVISORY PATENT EXAMINER

Notice to Comply	Application No. 10561826	Applicant(s) Verfaillie et al.	
	Examiner Chang-Yu Wang	Art Unit 1649	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:.

Applicant Must Provide:

An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application.**

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-0731 or (571) 272-0951
For CRF Submission Help, call (571) 272-2510
PatentIn Software Program Support
Technical Assistance.1-866-217-9197 or 703-305-3028 or 571-272-6845
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